Efficacy and Safety of Firsekibart in Patients With Acute Gout Unsuitable for Standard Therapy: 48-Weeks Results From an Open-Label Extension of a Randomized Phase 3 Trial

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Supplementary Appendix.1

Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for inclusion in this study:

1) Those who can voluntarily sign the informed consent form and voluntarily cooperate to complete the trial according to the protocol;
2) Age between 18 and 75 years old, both male and female;
3) Body Mass Index (BMI) ≤ 40 kg/m²;
4) Patients diagnosed with gout according to the 2015 American College of Rheumatology (ACR) gout classification criteria;
5) Had ≥ 2 acute gout attacks within 1 year before screening;
6) The current acute gout attack occurred within 4 days before the screening period;
7) The pain degree of the target joint during the screening period visual analog scale (VAS) ≥ 50 mm (VAS pain score 0-100mm);
8) There is evidence that the patient has contraindications and/or intolerance and/or lack of efficacy to Non-steroidal anti-inflammatory drugs (NSAIDs) and/or colchicine;
9) Willing to follow the ULT (urate lowering therapy) regimens during the study period, meeting one of the following conditions:
    a) Patients who are currently receiving ULT and have been stably treated for ≥ 14 days, and need to maintain a stable dosing regimen for at least 12 weeks during the trial, unless the investigator assesses that the patient has developed intolerance, poor efficacy or achieved the target uric acid level with the original ULT regimen, and allows adjustment of the ULT regimen including changing drugs, reducing dosage or discontinuing the treatment;
    b) Patients who have not used ULT before randomization are not allowed to take ULT within 14 days after randomization. After 14 days, the investigator will decide whether to take ULT based on the uric acid level. In principle, allopurinol is not selected for ULT;
    c) Patients who have used ULT but have not been stably treated for 14 days before randomization are not allowed to take ULT within 14 days after randomization. After 14 days, the investigator will decide whether to take ULT based on the uric acid level. In principle, patients who have not used allopurinol before are not allowed to use allopurinol for ULT in this study.

Exclusion Criteria

Patients with any of the following were not to be enrolled in the study:

1) A history of allergic reactions to the study drug or similar drugs;
2) Those who have received any of the following drugs or treatments within the specified time periods before randomization:
   - Ibuprofen or acetaminophen within 4 hours;
   - Diclofenac, tramadol, or local ice packs/cold packs within 6 hours;
   - Celecoxib, naproxen, loxoprofen, codeine, or colchicine within 12 hours;
   - Prednisone ≥ 10 mg or equivalent doses of corticosteroids within 24 hours;
   - Meloxicam, etoricoxib, or other short-acting analgesics within 24 hours;
   - Long-acting opioid treatment within 14 days before screening;
   - Intra-articular injection of glucocorticoids within 14 days before screening;
   - Prednisone ≥ 5 mg/d or equivalent doses of corticosteroids for more than 28 days within 12 weeks before screening or continuously within 14 days before screening;
   - Any IL-1 blockers, TNF inhibitors, or other biologics within 30 days before screening or within 3 half-lives (whichever is longer, or as per local regulations);
   - Systemic immunosuppressant treatment for more than 3 months before screening.
3) Those with active bleeding disorders of visceral organs, severe bleeding tendencies (such as hemophilia, etc.), or those undergoing anticoagulation treatment with heparin;
4) Those diagnosed with secondary gout (such as gout caused by chemotherapy, lead, transplantation, etc., except for gout caused by impaired renal function);
5) Those diagnosed or suspected of having rheumatoid arthritis, infectious/ septic arthritis, or other diseases that may confuse the assessment of affected joints, such as other pain conditions, including but not limited to neurological diseases, nerve root compression caused by intervertebral disc protrusion, herpes zoster, sciatica, etc.;
6) Those with infections requiring systemic medication control within 7 days before screening;
7) Those who have received live or attenuated live vaccines within 3 months before screening or plan to receive such vaccines during the study;

8) Those who have received the COVID-19 vaccine within 2 weeks before screening;
9) Those who have had cancer within 5 years before screening, except for adequately treated or surgically removed basal cell carcinoma of the skin or stage I squamous cell carcinoma;
10) Those who have received total body irradiation or total lymphoid irradiation treatment in the past; those who have received stem cell therapy or any type of bone marrow transplantation in the past; those who have received solid organ transplantation in the past; those who have received long-term systemic immunosuppressant treatment;
11) Those with a history of severe immunodeficiency, including: positive human immunodeficiency virus (HIV) antibodies; or other acquired or congenital immunodeficiency diseases;
12) Those with the following clinically significant diseases:
    - A history of chronic congestive heart failure, NYHA class IV; a history of echocardiographic detection of ejection fraction (EF) < 30%;
    - Myocardial infarction, acute coronary syndrome, viral myocarditis, or pulmonary embolism within 6 months; coronary revascularization within 6 months;
    - Severe arrhythmias requiring treatment with Class Ia or III antiarrhythmic drugs; arrhythmias such as sick sinus syndrome, second-degree type II or third-degree atrioventricular block without pacemaker implantation;
    - QTc interval ≥ 480 ms on the screening electrocardiogram (according to the Fridericia correction formula, where QTc = QT/(RR^0.33)), or a history of prolonged QTc interval.
13) Those meeting one of the following conditions may be included:
    a) Confirmed active tuberculosis infection: including but not limited to active tuberculosis infection confirmed by imaging;
    b) In the latent tuberculosis infection period or with high-risk factors for tuberculosis infection may be included, but patients deemed unsuitable for inclusion by the investigator, such as those unwilling to continue anti-TB treatment according to local guidelines after entering the trial, etc., should be excluded;
14) Those receiving renal dialysis;
15) Abnormal laboratory test values during the screening period:

- White blood cell count or absolute neutrophil count is lower than the lower limit of the normal range detected by the research center;
- Platelet count (PLT) ≤ 100 × 10^9/L;
- Total bilirubin > 1.5 × upper limit of normal (ULN), alanine aminotransferase (AST) > 3 × ULN, aspartate aminotransferase (ALT) > 3 × ULN;
- Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2;
- Triglycerides > 5.7 mmol/L;

16) Women with positive blood HCG during the screening period; women in the lactation period;
17) If the subject is female and does not agree to use adequate and effective contraceptive measures from the signing of the informed consent form to 6 months after the last dose of the drug, except for subjects who are menopausal or have undergone hysterectomy.
18) Having used investigational drugs or participated in other clinical trials within one month prior to screening;
19) Has a history of drug and/or alcohol abuse and/or mental disorders;
20) Other conditions or circumstances under which investigators deem the subjects unsuitable to continue participation in the trial.

Evidence of contraindications, intolerance, or lack of efficacy of NSAIDs and/or colchicine

A. Contraindication to NSAIDs (one of the following criteria must be met)

1) Allergic reaction to NSAIDs
2) Patients with asthma, urticaria, or anaphylactoid reactions after taking aspirin or NSAIDs
3) Cardiovascular disease (e.g., coronary artery bypass graft surgery, myocardial infarction, congestive heart failure, etc.)
4) History of peptic ulcer
5) History of gastrointestinal bleeding
6) Moderate or severe renal impairment

B. Intolerance to NSAIDs (must meet one of the following criteria)

1) Gastrointestinal reactions (e.g., nausea, dyspepsia, diarrhea, etc.)
2) Renal function decreased
3) Central nervous system reaction (e.g., headache, dizziness)
4) Hypertension (new or worsening)
5) Hepatotoxicity (increased ALT and/or AST)

C. Lack of Efficacy for NSAIDs (must meet one of the following criteria)

1) Failure of at least two NSAIDs attempted
2) Loss of efficacy after long-term treatment

D. Contraindications to colchicine (must meet one of the following criteria)

1) Known hypersensitivity to the drug
2) Severe gastrointestinal disease, including irritable bowel syndrome
3) Severe cardiac disease
4) Severe renal disease
5) Severe hepatic disease
6) Chronic use of HMG-CoA reductase inhibitors (e.g., atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, etc.) or fibrates (e.g., fenofibrate, bezafibrate, etc.)

E. Intolerance to colchicine (must meet one of the following criteria)

1) Myelosuppression, agranulocytosis, thrombocytopenia.
2) Peripheral neuropathy.
3) Arrhythmia.
4) Myopathy.
5) Vomiting, abdominal pain, nausea.
6) Diarrhea.

F. Lack of Efficacy for colchicine (must meet one of the following criteria)

1) Failure to relieve acute gouty pain when used for treatment
2) Failure to prevent acute attacks with appropriate dosing regimens
3) Insufficient/unsatisfactory pain relief
4) Loss of efficacy after long-term treatment

Table S1. Summary of TEAEs (48 weeks) with an incidence ≥5% in single vs repeat dosing.

System organ class and preferred term, n (%)	Single dosing		Repeat dosing	
	Firsekibart group (N=90)	CB group (N=70)	Firsekibart group (N=66)	CB group (N=86)
All TEAEs	79 (87.8)	63 (90.0)	61 (92.4)	76 (88.4)
Metabolism and nutritional disorders				
Hypertriglyceridemia	35 (38.9)	25 (35.7)	26 (39.4)	30 (34.9)
Hypercholesterolaemia	15 (16.7)	12 (17.1)	13 (19.7)	15 (17.4)
Hyperlipidaemia	5 (5.6)	3 (4.3)	10 (15.2)	10 (11.6)
Hyperglycaemia	1 (1.1)	0	6 (9.1)	1 (1.2)
Investigations				
Alanine aminotransferase increased	14 (15.6)	8 (11.4)	12 (18.2)	5 (5.8)
Blood creatinine increased	9 (10.0)	2 (2.9)	7 (10.6)	3 (3.5)
Blood creatine phosphokinase increased	7 (7.8)	9 (12.9)	4 (6.1)	5 (5.8)
Aspartate aminotransferase increased	6 (6.7)	1 (1.4)	6 (9.1)	4 (4.7)
Low density lipoprotein increased	5 (5.6)	2 (2.9)	1 (1.5)	0
White blood cell counts increased	3 (3.3)	9 (12.9)	3 (4.5)	0

Neutrophil count increased	0	5 (7.1)	4 (6.1)	0
Gamma-glutamyl transferase increased	3 (3.3)	2 (2.9)	5 (7.6)	5 (5.8)
Weight decreased	0	3 (4.3)	5 (7.6)	4 (4.7)
Infections and infestations				
Upper respiratory tract infection	8 (8.9)	7 (10.0)	13 (19.7)	17 (19.8)
Respiratory, thoracic and mediastinal disorders				
Cough	5 (5.6)	3 (4.3)	2 (3.0)	2 (2.3)
Hepatobiliary disorders				
Hepatic function abnormal	5 (5.6)	6 (8.6)	9 (13.6)	6 (7.0)
Musculoskeletal and connective tissue disorders				
Arthralgia	0	4 (5.7)	0	1 (1.2)
Back pain	2 (2.2)	0	6 (9.1)	2 (2.3)
General disorders and administration site conditions				
Pyrexia	1 (1.1)	4 (5.7)	0	7 (8.1)
Blood and lymphatic system disorders				
Anemia	0	1 (1.4)	1 (1.5)	5 (5.8)

CB, compound betamethasone; TEAE, treatment-emergent adverse event.

Table S2. Summary of TRAEs (48 weeks) with an incidence of ≥5% in single vs repeat dosing.

System organ class and preferred terms, n (%)	Single dosing		Repeat dosing	
	Firsekibart (N=90)	CB group (N=70)	Firsekibart group (N=66)	CB group (N=86)
All TRAEs	54 (60.0)	37 (52.9)	43 (65.2)	53 (61.6)
Metabolism and nutrition disorders				
Hypertriglyceridemia	26 (28.9)	16 (22.9)	20 (30.3)	20 (23.3)
Hypercholesterolaemia	10 (11.1)	5 (7.1)	7 (10.6)	11 (12.8)
Hyperlipidaemia	4 (4.4)	2 (2.9)	8 (12.1)	9 (10.5)
Investigations				
Alanine aminotransferase increased	4 (4.4)	3 (4.3)	9 (13.6)	3 (3.5)
Blood creatinine increased	6 (6.7)	0	2 (3.0)	1 (1.2)
White blood cell counts increased	1 (1.1)	8 (11.4)	0	7 (8.1)
Aspartate aminotransferase increased	3 (3.3)	0	6 (9.1)	0
Neutrophil count increased	0	5 (7.1)	0	5 (5.8)
Hepatobiliary disorders				
Hepatic function abnormal	0	4 (5.7)	3 (4.5)	5 (5.8)

CB, compound betamethasone; TRAE, treatment-related adverse event.

Control group 2 comprised post-crossover data of patients who crossed over from CB.